UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/076,404	05/12/1998	DAVID J. ECKER	IBIS-0007US	4802

52315 7590 08/05/2010

Pepper Hamilton LLP
400 Berwyn Park
899 Cassatt Road
Berwyn, PA 19312-1183

EXAMINER	
BRUSCA, JOHN S	
ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
08/05/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DAVID J. ECKER, RICHARD GRIFFEY,
STANLEY T. CROOKE, RANGA SAMPATH,
ERIC SWAYZE, VENKATRAMAN MOHAN,
STEVEN HOFSTADLER, and JOHN MCNEIL

Appeal 2010-002912
Application 09/076,404
Technology Center 1600

Before ERIC GRIMES, LORA M. GREEN, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

---

[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's rejection of claims 19, 20, 26, 30, 32-35, 37, 38, 40, 41, 43, 44, 46, and 47. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

Claims 19 and 26 are representative of the claims on appeal, and read as follows:

19. A method of identifying a compound that binds to a human target RNA comprising:

generating *in silico* a virtual library of compounds and an *in silico* three dimensional representation of a molecular interaction site within said human target RNA, wherein the molecular interaction site is less than 30 nucleotides;

comparing *in silico* said three dimensional representations of said molecular interaction site with members of the virtual library of compounds to generate a hierarchy of said compounds ranked in accordance with their respective ability to form physical interactions with said molecular interaction site;

synthesizing the highly ranked members of said hierarchy of compounds; and

testing said highly ranked members to determine their ability to interact with said molecular interaction site by:

contacting the human target RNA with at least one of said highly ranked members to provide a complex between the human target RNA and the member or members;

ionizing said complex;

fragmenting the ionized complex; and

determining whether highly ranked members bind to the molecular interaction site of said human target RNA; and

thereby identifying said compound that binds to a human RNA target.

26. A method of identifying a compound that binds to a human target RNA comprising:

identifying *in silico* at least one molecular interaction site less than 30 nucleotides in length on said human target RNA by comparing the nucleotide sequence of said human target RNA with the nucleotide sequence of a RNA from a different taxonomic species;

identifying at least one conserved region, and determining the secondary structure of said conserved region;

generating *in silico* a virtual library of compounds predicted or calculated to interact with said molecular interaction site;

comparing *in silico* three dimensional representation of said molecular interaction site with members of the virtual library of compounds to generate a hierarchy of said compounds ranked in accordance with their respective ability to form physical interactions with said molecular interaction site;

synthesizing the highly ranked members of said hierarchy of compounds;

testing said highly ranked members to determine their ability to interact with said molecular interaction site;

contacting said human target RNA with at least one of said highly ranked members to provide a complex between said human target RNA and the member or members;

ionizing said complex;

fragmenting the ionized complex; and

determining whether highly ranked members binds to the molecular interaction site of said human target RNA; and

thereby identifying; said compound that binds to a human RNA target.

Claims 19, 20, 26, 30, 32-35, 37, 38, 40, 41, 43, 44, 46, and 47 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Murray,[2] Arenas,[3] Sezerman,[4] Greig,[5] and Hentze.[6]

---

[2] Murray et al., *PRO_SELECT: Combining structure-based drug design and combinatorial chemistry for rapid lead discovery. 1. Technology*, 11 JOURNAL OF COMPUTER-AIDED MOLECULAR DESIGN 193-207 (1997).

[3] Arenas et al., US 6,337,183 B1, issued Jan. 8, 2002.

[4] Sezerman et al., *Toward computational determination of peptide-receptor structure*, 2 PROTEIN SCIENCE 1827-1843 (1993).

We affirm.

ISSUES

Has the Examiner established by a preponderance of the evidence that the combination of Murray, Arenas, Sezerman, Greig, and Hentze renders the methods of claims 19 and 26 obvious?

FINDINGS OF FACT

FF1 We adopt the Examiner's findings of fact in the statement of the rejection as our own. (Ans. 4-6.)

FF2 Appellants argue the claims in two groups: Group I comprising claims 19, 20, 32-35, 37, 38, 43, 44, 46 and 47, of which we choose claim 19 to be representative; and Group II comprising claims 26, 30, 40, and 41, of which we choose claim 26 to be representative. (*See* App. Br. 12.) We also make the following additional findings of fact.

FF3 Murray describes what they term the "PRO_Select" methodology, "which combines elements of structure-based drug design and combinatorial chemistry to create a new paradigm for accelerated lead discovery." (Murray, Abstract.)

---

[5] Greig et al., *Measurement of Macromolecular Binding Using Electrospray Mass Spectrometry. Determination of Dissociation Constants for Oligonucleotide-Serum Albumin Complexes*, 117 J. AM. CHEM. SOC. 10765-10766 (1995).

[6] Hentze et al., *Identification of the Iron-Responsive element for the Translational Regulation of Human Ferritin mRNA*, 238 SCIENCE 1570-1573 (1987).

FF4 The procedure consists of the steps of 1) constructing a virtual combinatorial library based around a template chemistry appropriate for the target molecule and amenable to combinatorial synthesis; 2) screening the members of the library based on their interaction with a target receptor; and 3) synthesis and testing of representative elements of the library as single compounds. (*Id.* at 194, second column.)

FF5 Thus, in designing thrombin inhibitors, Murray selected 30 molecules based on the *in silico* screening methods to synthesize and test for activity. (*Id.* at 204, second column.)

FF6 Sezerman reports a computational method for docking small flexible ligands. (Sezerman, Abstract.) Sezerman also discusses applying the method to peptide-MHC-class I systems, noting that the "predictions are in accord with biological and crystallographic data." (*Id.*)

FF7 Hentze identified the "iron-responsive element" (IRE) by deletional analysis. (Hentze, Abstract.)

FF8 Hentze predicts, based on computer-modeling, that the core region identified using the deletional analysis should have a stem-and-loop structure. (*Id.* at 1571, third column.)

FF9 Hentze then compared the core region to cDNA sequences from other species, concluding that "the core region has been highly conserved during evolution." (*Id.* at 1572, middle column.)

PRINCIPLES OF LAW

While the analysis under 35 U.S.C. § 103 allows flexibility in determining whether a claimed invention would have been obvious, *KSR*

Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418 (2007), it still requires showing that "there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* "We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008).

Thus, while holding that some rationale must be supplied for a conclusion of obviousness, the Supreme Court nonetheless rejected a "rigid approach" to the obviousness question, and instead emphasized that "[t]hroughout this Court's engagement with the question of obviousness, our cases have set forth an expansive and flexible approach . . . ." *KSR*, 550 U.S. at 415. The Court also rejected the use of "rigid and mandatory formulas" as being "incompatible with our precedents." *Id.* at 419; *see also id.* at 421 ("Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it.").

The Court thus reasoned that the analysis under 35 U.S.C. § 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418; *see also id.* at 421.

ANALYSIS

As to Group I, Appellants argue that "a major goal of the Murray reference is to provide an *in silico* method, rather than actual physical methods, of predicting binding of a potential therapeutic compound to a particular receptor," reporting "identification of thrombin inhibitors by a completely *in silico* method, in contrast to actually carrying out physical binding assays." (App. Br. 15.) Appellants thus assert that "[a]ny modification of the Murray reference that would add another layer of a completely different, let alone physical, technology such as mass spectrometry, would be counter to the *in silico* methodology of the Murray reference." (*Id.*)

Appellants argue further that Sezerman "uses an entirely *in silico* methods to dock ligands to a receptor and calculate the interaction energy of such docking," and does not teach or suggest using a bench method of looking at binding affinity, such as mass spectrometry. (*Id.* at 14-15.) Appellants assert that replacement of the computational method of Sezerman with a mass spectrometric method "is nonsensical and defeats a goal of the Sezerman reference," and thus the only way in which the method of claim 19 can be rendered obvious over that reference is through the use of impermissible hindsight. (*Id.* at 15.)

Appellants' arguments are not convincing. Murray teaches computationally screening a virtual library of compounds, and based upon the results of that computational screening, choosing compounds for actual synthesis and screening. Thus, Murray demonstrates that it is well known to

the ordinary artisan to combine computational methods with bench methods to test the predictions made by the computational methods.

As to Group II, of which claim 26 is representative, Appellants argue that the references do not teach individually or combined, the steps of

> identifying *in silico* at least one molecular interaction site less than 30 nucleotides in length on said human target RNA by comparing the nucleotide sequence of said human target RNA with the nucleotide sequence of a RNA from a different taxonomic species; [and] identifying at least one conserved region, and determining the secondary structure of said conserved region

as required by the method of claim 26. Appellants assert that Hentze, relied upon by the Examiner for teaching those steps, actually identifies the iron-responsive element (IRE) by deletional analysis, and not by comparing a nucleotide sequence of said human target RNA with the nucleotide sequence of a RNA from a different taxonomic species, as required by claim 26.

The Examiner responds that Hentze compares the IRE to that in other taxonomic species, and thus "identified a conserved domain, which is in agreement with the mapping of the domain by progressive deletional analysis." (Ans. 7.)

We conclude that the Examiner has the better position. The method of claim 26 uses the transition term "comprising," and thus does not exclude additional steps, such as the deletional analysis performed by Hentze. Specially, Hentze used the results of the deletional analysis to identify using computational methods the presence of the conserved region in other taxonomic species, and thus teaches all of the method steps required by claim 26.

CONCLUSIONS OF LAW

We conclude that the Examiner has established by a preponderance of the evidence that the combination of Murray, Arenas, Sezerman, Greig, and Hentze renders the methods of claims 19 and 26 obvious.

We thus affirm the rejection of claims 19, 20, 26, 30, 32-35, 37, 38, 40, 41, 43, 44, 46, and 47 under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Murray, Arenas, Sezerman, Greig, and Hentze.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc

PEPPER HAMILTON LLP
400 BERWYN PARK
899 CASSATT ROAD
BERWYN PA 19312-1183